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Eye-catching: The beauty of a highly metastable form of paracetamol is revealed when viewed between crossed polarizers on a hot-stage microscope.

The Right Stuff

From research and development to the clinic, getting drug crystals right is full of pitfalls

The next time you must swallow a drug tablet, take a moment to inspect it. It is whole? Dust free? Is it uniform in composition? Very likely, you'll find every time that it is. We expect tablets to be like that, and we take them without second thoughts. Yet to produce something as prosaic as a tablet requires chemical and engineering decisions that must take into account not only safety, efficacy and processability, but also defensibility of intellectual property.

The drug substance is the most important ingredient in that tablet but not necessarily the one in greatest amount; other components, called excipients, make up the rest. Most drug substances – or active pharmaceutical ingredients (APIs) – are solid organic compounds, even though the final drug product may be in liquid form. Thus, the formation of solids of uniform properties is critical in API production. Failure to do so can be devastating.

The case of ritonavir, Abbott Laboratories' drug for patients with AIDS, is well known. The drug was formulated as an encapsulated solution in ethanol/water. In the summer of 1998, supplies were threatened when a new crystal form appeared, first at a production plant in North Chicago, and then at a plant in Italy. Ritonavir was the victim of a late-appearing polymorph with different solubility properties.

Polymorphs arise when molecules of a compound stack in the solid state in distinct ways. Although identical in chemical composition, polymorphs can have very different properties. They are distinguishable by various analytical techniques, especially X-ray powder diffraction. In addition, solids may form solvates and hydrates, also called pseudopolymorphs.

Polymorphs tend to convert from less stable to more stable forms. The rate of conversion depends on the required activation energy and the differences in free energies, says Wayne J Genck, president of Genck International, an industrial consulting group based in Richton Park, Illinois, that specialises in crystallization and precipitation. But no method yet exists to predict the polymorphs of a solid compound with significant certainty. The search for polymorphs is largely an empirical exercise. "It is still not possible to figure out how many different ways a molecule can lie down with itself in a lattice," says Jerry L Atwood, a chemistry professor at the University of Missouri, Columbia. "Small-molecule drugs are very

flexible. There's no way to tell what a large floppy molecule can do in the solid state except by doing experiments. It gets worse when you might consider that this molecule might have non-obvious binding sites for solvent molecules."

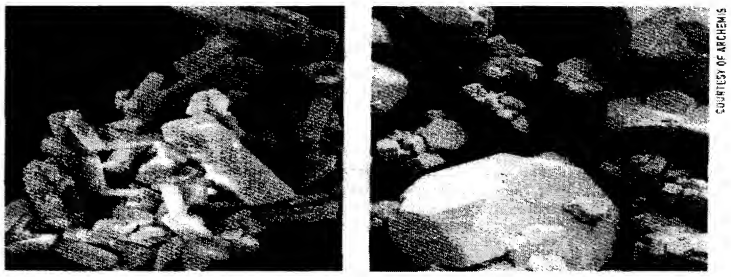
Predictive software systems are available but are restricted in the size and elemental compositions of the molecules they can handle, says G Patrick Stahly, chief operating officer of SSCI, a West Lafayette, industrial-based cGMP (current Good Manufacturing Practice) contract research laboratory. It specialises in chemistry, crystallization and characterisation of solid materials. "Even when crystal structures can be predicted, the relatively small energy differences between polymorphs make it difficult to predict which calculated structures are likely to be real," he adds.

It is best to work with the most stable polymorph – also called the ground state form – because it will not convert any further. But the ground state usually is the least soluble. To improve bioavailability, drug companies sometimes trade off polymorph stability with solubility, "recognising that they will have to deal with the possibility of an undesired conversion to a more thermodynamically stable form," Genck says.

On the other hand, Stahly says that much effort is being expended looking for metastable forms of currently marketed drugs whose stable forms have been around for a long time. For innovator companies, new forms offer the possibility of introducing improved drug products. For generic companies, new forms present an opportunity to make generic versions of brand-name products more quickly.

When polymorph conversion occurs, it may be impossible to reproduce the less stable form. It just disappears. Tales of disappearing polymorphs abound. Evelyne Chassagneux, director of business development at Archemis, a French contract development organisation, recalls a drug candidate for which Phase I clinical trials had just been completed when a new polymorph appeared. "The properties changed, and we never recovered the old form," she tells C&EN. Fortunately, the conversion occurred at an early stage in development. "The lost form was not registered. If it had been registered, all the work would have had to be redone. That would have been a disaster."

Furthermore, in this case, the late-appearing polymorph fortuitously had better processing qualities. "The old crystals were needle-like, very sticky, with lots of static electricity," Chassagneux says. "The new form was easier to formulate."



Good luck: the disappearance of the polymorph characterised by needle-like particles and poor flowability (left) upon formation of the polymorph characterised by big-faceted crystals and good processability was fortuitous.

The outcomes from ritonavir were different. From solubility and manufacturing perspectives, the old form was superior to the new form, and Abbott process chemists worked mightily to recover it. Not only did they develop a method that ensured consistent production of the old form only, but they also found a way to convert the new form to the old form.

San Kiang, director for process R&D at Bristol-Myers Squibb's Pharmaceutical Research Institute, New Brunswick, New Jersey, tells about a similar outcome for a compound that had been in development for 10 years. "The sky dropped one day – a new polymorph was discovered I the pilot plant," he says. In this case, putting the pilot plant under quarantine and imposing manufacturing protocols like those for operating under sterile conditions allowed production of the old form to continue, he says. The drug product now in the market contains the original polymorph, he adds.

"Different polymorphs differ in bioavailability, solubility, dissolution rate, chemical and physical stability, melting point, colour, filterability, density and flow properties, among others," Stahly says. The difference in solubility can affect drug efficacy, bioavailability and safety.

Stahly cites a case in which test animals survived the first toxicological test of a drug candidate but died in the second. "Subsequent analysis showed that the first test was carried out using a crystalline form of the drug and the second using an amorphous form," he says. "Amorphous forms can be up to 1,000 times more soluble tan the crystalline form," he explains. Because of that solubility advantage, amorphous forms are preferred for some formulations, such as drugs that will be reconstituted to an injectable solution. But because the amorphous form is always under thermodynamic pressure to crystallize, a frequent problem is crystallization over time.

In another example, a change in the equipment used to dry the final drug substance gave a product that had inferior handling and filtering properties than what the manufacturer was used to. The new drying equipment was causing the formation of hydrates. "This case is interesting because it shows that control of form was occurring at the drying stage," Stahly says. "That's one of the last places people look. Most people think that the critical stage is when the crystals come out of solution. But there are many places after crystallization where changes can occur," he explains.

Polymorphs are also important in formulation and storage, according to Rolf Hilfiker, head of the physical chemistry business unit of Solvias, the Basel, Switzerland-based custom research company that was spun off from Novartis. Some polymorphs are more difficult to formulate than others because of their shape or hygroscopicity. And "what's really important during storage is not to have a conversion from one form to another. Otherwise, your tablet with turn either into powder or into concrete. It won't have the same bioavailability anymore," he says.

Even with intermediates for API synthesis, polymorphism is an issue, says Genck. Although intermediates eventually end up being dissolved – and once they are dissolved, polymorphism is no longer an issue – they are supplied as solids. At this state, the issue is not so much stability but processability, Genck says. Metastable forms sometimes reject impurities and filter better than the most stable polymorph.

Kiang recalls a recent incident in the manufacture of an intermediate. "One of the impurities had always been an oil," he explains. "It never crystallized, so it was easily eliminated during processing. But one day, it crystallized and became an impurity in the product. It took a lot of process redesigning to eliminate this new crystal, which had never formed before."

Despite the compelling case for polymorphism studies early in drug development, the practice is not standard in the pharmaceutical industry. "There are two types of companies," Chassagneux says. "Those that have already experienced problems do the studies very early. They have learned their lesson. The others don't pay attention. When they have problems, they ask us to troubleshoot."

The pharmaceutical industry has not really had a good handle on issues of crystallization and polymorphism, says Allan S Myerson, a professor of chemical engineering at Illinois Institute of Technology, Chicago. Myerson directs the Particle Technology & Crystallization Centre at IIT. The centre is a collaboration of IIT, Purdue University and Massachusetts Institute of

Technology that was established last year to address basic problems in crystallization and particle technology relevant to the pharmaceutical industry.

"We're focusing our effort on the API", Myerson says. "That includes polymorphism, crystal shape, crystal size, understanding what data are required on a very small scale to make the same material repeatedly on a larger scale, interaction of API with excipients and how unit operations – such as granulation, compaction and tableting – affect crystal structure."

The centre is funded by subscriptions from member companies, which as present number three: Abbott, Aventis and Bristol-Myers Squibb, Myerson says. Currently, three projects are under way: developing methods for seeding, evaluating techniques for online sensing of crystallization parameters and studying the interaction of APIs with excipients.

Drug companies have urgent reasons to systematise knowledge in these areas, Myerson says. First, the Food & Drug Administration has become very strict about API form, shape and size distribution, especially after the generic drug scandal of the late 1980s. Patients taking some generic drugs were not getting the therapeutic effect because the API in the generic version was a different polymorph and had poorer solubility and bioavailability than that in the brand-name drug.

Second, mistakes can cost hundreds of millions of dollars.

Ritonavir is well known, but many other cases of new polymorphs appearing at late stages are not made public, Myerson says. "It is very expensive to go back, reformulate and do your testing again."

Companies constantly have scale-up problems, often because they haven't done the correct experiments on a small scale and they don't have the appropriate fundamental data for developing a crystallization process, Myerson says. "It's shocking sometimes, but drug companies have so many precandidate compo9unds that the strain in getting data early has led them to not get as much. When suddenly one of these compounds becomes hot and they have to make more of it, they go without basic data."

And third, polymorphs have patent implications.

Polymorphs can be patented if they can be shown to have better properties than others, Hilfiker says. For maximum patent protection, drug companies usually patent the compound first, and then they do the studies to find the polymorphs and patent those as well. "It's dangerous to wait too long because somebody else can come in and patent the good polymorphs first," he adds.

Polymorphs and pseudopolymorphs have been central to a number of legal cases between innovator and generic drug companies. For example, efforts by GlaxoSmithKline to protect the antidepressant Paxil (paroxetine hydrochloride) from generic competition have been based in part on separate patents claiming anhydrous and hemihydrate forms of the drug substance. Similarly, GSK has claimed extended patent protection of the acid reflux drug Zantac (ranitidine hydrochloride) on the basis of a new crystal form patented eight years after the drug substance patent was issued.

In another example, Bristol-Myers Squibb sued a generic company marketing a hemihydrate of the antibiotic cefadroxil, BMS claims the monohydrate in a patent, and it sued on the basis that the hemihydrate converts into the monohydrate transiently before it dissolves. "To most scientists, realising that the drug itself is undoubtedly not hydrated when it is in the active site and doing its job, this argument is highly creative," Atwood notes. The case was decided against BMS because it did not prove that the conversion in vivo occurs as claimed.

These cases underscore the difficulty of properly characterising compositions of matter so that a patent not only claims as much as possible and substantiates all the areas under the claim, but also protects the intellectual property from attack. Typically, the scientist writes

up the invention, and the legal team takes the lab notebook and translates the invention into a patent, Atwood says. If the legal team does not understand the subtle nuances of the scientist's methods, the product will be vulnerable to attack. It is precisely at that time when non one yet knows whether a patent may be worth billions – or nothing – when a few dollars and some outside help can save a blockbuster from attack in later years, he says.

Polymorphs have some much impact that it makes sense to do polymorphism studies early on, Hilfiker says. "We advise a small study at preclinical development and a large study before clinical studies.

Compared with the total cost of drug development, the cost of polymorph screening is miniscule: $25,000 to $100,000, depending on the scope. Stahly says. The experiments are designed to encourage the production of different forms based on variations in nucleation and growth conditions. A screen than incorporates impurities and degradation products is recommended for drug candidates in an advanced stage of development.

"The primary lesson we took from the ritonavir case was that the effects of impurities and degradation products should be investigated during screening," Stahly says. That's because Abbott chemists showed that the late-forming polymorph was induced by the presence of ritonavir degradation product with a very similar conformation.

Scrutiny: the search for polymorphs requires rigorous visual inspection.

Screening can never give 100% of the possible polymorphs. As many in the field like to say, the number of polymorphs increases with the length of time a compound is under scrutiny. "It's not just that the screening fails," Bristol-Myers Squibb's Kiang explains. "When you're optimising the process to make the active substance, you are changing chemicals and reaction conditions. Those changes in the normal course of development may surprise you with a new polymorph that didn't show up in the screen."

Kiang offers a simple strategy to minimise the possibility of late-appearing polymorphs: Fix the last step first. "You know your target from day one," he says. "How to get there is up to the imagination of the chemist. But you decide at the outset what the final chemical step will be, and you can design it to be as chemically simple as possible and optimise conditions to get the same polymorph every time."

If you can't fix the final step, then add a recrystallization step, Kiang says. "It sounds redundant, and you always lose yield with each step," he adds. "But for some compounds, such as the very potent compounds that must be formed as very fine particles, it may be the best approach."

Various techniques and strategies are available to get particles of desired characteristics. "I call it particle engineering," Kiang says. "Given the salt form, the polymorph, the requirements of the formulation, ask yourself what are the desired properties of the crystals. We now have various techniques and approaches to achieve those properties through crystallization."

Particles of submicrometre size can be achieved with very fast mixers and high-shear mixers. Additives may be added during crystallization to modify the crystal shape for

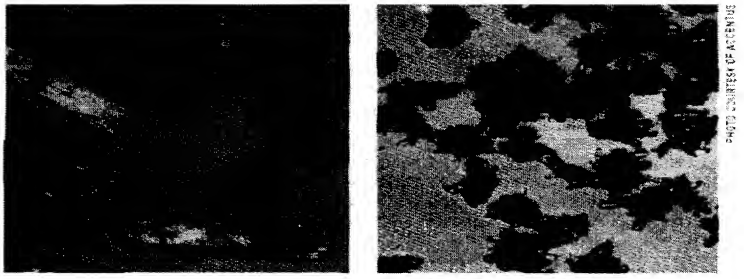
processability. "Most drug substances crystallize as needles," Kiang explains. "Needles don't flow very well, but we can force them to change shape through engineering."

Another tool is available from Accentus, Abingdon, UK: a scaleable, non-invasive technology to control crystal habit and size distribution based on ultrasound.

Sonocrystallization – or crystal formation through ultrasound – has been around for a long time in the lab, says Linda J McCausland, Accentus chief technologist. The problem has been in scaling up systems based on metal probes sticking into crystallizers. "That doesn't work because you tend to get hotspots," she says. "The ultrasound is thrown just a couple of centimetres from the probe tip instead of throughout the reactor. Plus, the probe erodes, giving all kinds of contamination problems."

In the Accentus design, ultrasound is delivered through transducers bonded onto the outside walls of a flow cell. The flow cell may be configured with the crystallizer in two ways. In a batch mode, it is connected through a tube through the crystallizer lid. When the crystallizer contents are ready for seeding, an aliquot is sent up to the flow cell by vacuum or pressure and treated for the period required to form the desired crystal seeds. Then the seeds are dropped back to the bulk. This set-up is used when the goal is to use ultrasound to produce seed crystals only.

In a continuous mode, the flow cell is connected to the crystallizer in a loop. Material from the bulk enters the loop, is treated in the flow cell, and then circulates back to the crystallizer. This set-up is used when the bulk needs to be treated with ultrasound to control size distribution. McCausland says both modes have been scaled up to 4,500 L.



Control: crystals formed by ultrasound-initiated nucleation (left) are better defined and more processible than those produced without ultrasound. (Photos taken under the same magnification).

According to Peter W Cains, a senior chemist at Accentus, there is evidence that use of ultrasound to nucleate potentially polymorphic systems likely forms either the ground state polymorph or one near the ground state. Where this can be very useful is when a drug candidate has been screened for polymorphs and a potential ground state has been identified. "We can run tests with ultrasound and see if we can get a more stable polymorph," McCausland says.

But Cains cautions: "You can never prove that any technique produces the ground state. In a lot of development projects, you don't know what the ground state is."

"The worst thing is bringing to market a metastable form and not knowing it," Hilfiker says, referring back to the ritonavir case. "If Abbott had known, it may not have used that form. Or it would have developed a process that would have precluded polymorph conversion."